

### **REMARKS**

Upon entry of the Amendment filed with a Request for Continued Examination on April 1, 2009 (herein, the "April 1 Amendment"), Claims 1, 3, 5-9 and 12-19 were pending in the application. In this Supplemental Amendment, Claims 1, 15, and 17 are amended. Claims 16 and 18 are cancelled herein. Upon entry of this Supplemental Amendment, Claims 1, 3, 5-9, 12-15, 17 and 19 are pending in the application. Claims 6-8, 13 and 17 are presently withdrawn.

### **EXAMINER'S INTERVIEW**

Applicant acknowledges and appreciates the courtesy afforded by Examiners Fernandez and Lankford in an interview conducted on May 11, 2009 with Applicant's representatives Fernando Alberdi and David Suter, and a technical expert, Dr. Paul D'Antonio, who is an employee of Applicant's assignee. Applicant also acknowledges the Interview Summary issued May 22, 2009, providing a summary of the subject matter discussed in the interview. Applicant thanks the Examiners for recognizing, in the interview, the existence of an invention and for discussing possible strategies for overcoming the rejections of record, as further discussed below. Applicant is filing this Supplemental Amendment to reflect the input from the Examiners, prior to further examination. Applicant has amended the claims to further define the type of repair and enhancement afforded by the pulsed electromagnetic field treated tissue culture medium when applied to bone, cartilage and wound defects, as discussed during the interview.

### **REJECTION UNDER 35 U.S.C. § 112**

Claims 1-5, 9, 10, 12, 14-16, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and under 35 U.S.C. §

112, first paragraph, as failing to comply with the enablement requirement. These rejections are respectfully traversed.

For the sake of brevity, Applicant restates the grounds for overcoming the written description and enablement rejections under 35 U.S.C. § 112, first paragraph set forth in the April 1 Amendment, and incorporates the arguments contained therein in their entirety. It is respectfully submitted, that these rejections under 35 U.S.C. § 112, first paragraph have been overcome by the previous amendments and arguments provided in the April 1 Amendment and the amendments provided herein.

#### **REJECTION UNDER 35 U.S.C. § 102**

Claims 9, 11, and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,195,940, Baylink, issued March 23, 1993 (herein "*Baylink*") and under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,334,069, George et al., issued December 25, 2001, (herein "*George*"). This rejection is respectfully traversed.

Applicant thanks the Examiner for addressing the 35 U.S.C. § 102(b) rejection under *Baylink* and §102(a) and §102(e) rejections under *George*, in view of the Applicant's amendment to recite tissue culture medium produced by pulsed electromagnetic stimulation of an endothelial cell tissue culture for at least about eight hours. Applicant understands that these anticipation rejections are overcome by the Applicant's amendment to Claim 9 submitted in the April 1 Amendment.

### **REJECTION UNDER 35 U.S.C. § 103**

Claims 1-5, 9, 10, 12, 14-16, and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,372,494, Naughton, issued April 16, 2002 (herein “*Naughton*”), in view of *Baylink* and/or *George* and further in view of Guerkov et al., Pulsed Electromagnetic Fields Increase Growth Factor Release by Nonunion Cells, *Clinical Orthopaedics and Related Research*. 2001. 384: 265-279 (herein “*Guerkov*”). In addition, Claims 1, 3, 9, 12, 14, and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over PCT International Application Publication WO 93/04164, Shipley, published March 4, 1993 (herein “*Shipley*”) in view of *Baylink* and/or *George* and further in view of *Guerkov*. These rejections are respectfully traversed and are discussed in combination.

During the Examiner’s Interview on May 11, 2009, Examiners Fernandez and Lankford commented that the claim clause “wherein said medium is capable of repairing or enhancing the bone or cartilage tissue defect” was not sufficient to distinguish the cited art. It was suggested that focusing on a specific effect, such as angiogenesis, could further distinguish the teachings of the art, however.

Accordingly, Applicant is amending the claims to more precisely state how the method of Claim 1 repairs and enhances the bone and cartilage defects, i.e. through the effect of angiogenesis. Similar language has been incorporated into Claim 15. The amendments to Claims 1 and 15 are supported by the specification as originally filed, for example, on page 1 of the originally filed specification, which describes the need to develop new methods of therapeutic angiogenesis as a mechanism for repair and growth of tissue. (See Application at page 1, par. [0002 and 0003]). Example 2 is drawn to the use of pulsed electromagnetic fields to induce and stimulate endothelial cells in microcarriers to form new tubules which are

representative of the physiologic processes undertaken during neovascularization and angiogenesis. Thus, one of ordinary skill in the art would readily recognize that the Applicant's specification describes therapeutic angiogenic processes, for example, induction of new blood vessels as a method to treat tissue defects, including bone, cartilage and wound defects.

Applicant respectfully submits that the amended Claims 1 and 15 clarify the invention which was recognized by the Examiners during the May 11 interview. The amended claims are not obvious from the teachings of *Naughton* or *Shipley* in view of *Baylink* and/or *George* and further in view of *Guerkov*.

In particular, *Guerkov* teaches away from administering a tissue culture medium derived from pulsed electromagnetic field treated cells to induce endothelial cell proliferation and stimulate angiogenesis in a bone or cartilage defect site. As argued in the April 1 Amendment, the cellular proliferation of non-union cells was not observed in *Guerkov* after application of pulsed electromagnetic field. *Guerkov* specifically teaches that production of TGF- $\beta$ 1 by the non-union cells was upregulated. TGF- $\beta$ 1, in turn, stimulates the cellular proliferation of fibroblasts but not endothelial cells.

TGF- $\beta$ 1 has long been known to inhibit endothelial cell proliferation and endothelial cell movement necessary for tubule formation and neovascularization in general. For example, *Sato* et al. experimentally determined that migration of bovine aortic endothelial cells is impaired due to the actions of active TGF- $\beta$ 1 consistent with the results of Frater-Schroeder et al. (1986) and Baird and Durkin (1986) which showed that TGF- $\beta$ 1 inhibited the proliferation of endothelial cells. (*Sato et al., (1989) "Inhibition Of Endothelial Cell Movement By Pericytes And Smooth Muscle Cells: Activation Of A Latent Transforming Growth Factor- $\beta$ 1-like Molecule By Plasmin During Co-Culture"* J. Cell Biol, Vol.109: 309-315, particularly at page 313, col. 2. (A copy of

*Sato et al.* is enclosed.) Accordingly, *Guerkov* teaches away from Applicant's invention, providing no basis for one of ordinary skill in the art to subject a culture of endothelial cells to an electromagnetic field, so as to produce a tissue culture medium capable of stimulating angiogenesis.

This distinction is reinforced in amended Claims 1 and 15, which require a tissue culture medium capable of inducing endothelial cell proliferation. Since all of the pending claim rejections under 35 U.S.C. § 103(a) rely on *Guerkov*, Applicant submits that the teaching away by *Guerkov* evidences the non-obviousness of all claims and overcomes the rejections of Claims 1, 9 and 15, as well as their dependent Claims 2-5, 10, 12-14, 18 and 19.

#### CONCLUSION

Applicant respectfully requests that the rejections under 35 U.S.C § 103(a) of Claims 1, 3, 9, 10, 12, 14, and 15 be reconsidered and withdrawn. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 241-1600.

Respectfully submitted,

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